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EXAMINER	
KELLY, ROBERT M	

ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/033,491	ZHANG ET AL.	
	Examiner	Art Unit	
	Robert M. Kelly	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *70-226* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *70-226* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's argument and amendments of 10/28/05 have been entered.

Claims 70, 72-73, 78, 101, 103-104, 109, 132, 134-135, 140, 163, 165-166, 171, 194, 196-197, 202, and 226 have been amended.

Claims 70-226 are presently pending and considered.

Claim Objections

Claims 149-150 are objected to because of the following informalities: Claims 149 and 150 depend from each other, however, it is clear that they should depend from claims 148 and 147, respectively. Because it is clear to the Examiner what Applicant intended, the claims not rejected, but objected to on this basis. Appropriate correction is required.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

In light of Applicant's filing of the terminal disclaimer of 10/28/05, the rejections of Claims 70-226 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 12 and 31 of U.S. Patent No. 6,726,907, are withdrawn.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 70-226 remain provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 13-28, 31, and 33-37 of copending Application No. 09/203,078, for reasons of record.

Double-Patenting over 09/203,078 held in Abeyance

In accord with Applicant's request, the provisional double-patenting rejection over U.S. Application No. 09/203,078 is maintained, but held in abeyance (Applicant's response of 4/11/05, p. 22, paragraph 5).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

In light of Applicant's filing of a terminal disclaimer on 10/28/05, the rejections of Claims 70-226 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-89 of U.S. Patent No. 6,194,191, are withdrawn.

Claim Rejections - 35 USC § 112, first paragraph, critical element

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 70-87, 91-118, 122-149, 153-180, 184-211, and 215-226 are rejected under 35 U.S.C. 112, first paragraph, as based on a disclosure which is not enabling. The presence of a therapeutic transgene is critical or essential to the practice of the invention, but not included in the claim(s) is not enabled by the disclosure. See *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976). Specifically, with regard to making adenoviral vectors, Applicant has taught that any adenoviral vector may be used, even without a transgene, e.g., p. 4, paragraph 1, and may

comprise any exogenous transgene, e.g., p. 4, last paragraph; however, with regard to therapeutic adenovirus compositions, Applicant has only taught that adenoviruses are contemplated to comprise a therapeutic gene (e.g., p. 5, paragraph 2). Hence, these claims are lacking critical or essential elements, i.e., a therapeutic transgene.

Claim Rejections - 35 USC § 112, second paragraph, essential element

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 70-87, 91-118, 122-149, 153-180, 184-211, and 215-226 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: the presence of a therapeutic transgene. The reasoning is the same with regard to the rejection for lacking critical elements under the first paragraph of 112, above.

Claim Rejections - 35 USC § 112 – New Matter

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 78, 109, 140, 171, and 202 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims encompass the limitation that the adenoviral composition be

"essentially free of BSA". Applicant argues that the specification provides support for such limitation on page 72, paragraph 2, where it says that the compositions should be essentially free of pyrogens as well as other impurities that could be harmful to humans or animals (Applicant's argument of 10/28/05, p. 2, paragraph 1). However, such does not equate to the scope Applicant claims, and the Examiner has only found implicit support for such limitation, in the form of a specific method which produces BSA levels below the detection limit of a western blot assay (EXAMPLE 6), hence, outside of the specific embodiment of making the virus in EXAMPLE 6, Applicant has no support for the wide breadth claimed.

Claim Rejections - 35 USC § 112 – Written Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

In light of Applicant's argument, the rejections of Claims 70-226 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, for "a therapeutic adenovirus", are withdrawn.

Specifically, it is clear that Applicant's invention is not a method of gene therapy, but a method of making adenoviruses, and the ONYX adenoviruses were known in the Art, and there exist no reason to believe these adenoviruses could not be grown in Applicant's methods. Moreover, although the Specification does not evince contemplation of the therapeutic adenovirus without a transgene, the originally filed claims encompass such embodiments, therefore, it appears that written description is provided. Hence, the rejection is withdrawn.

Claim Rejections - 35 USC § 112 - Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 70-226 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

A method of treating a patient for a tumor, comprising the art-recognized form of administration of the adenoviral vector encoding p53 operably linked to a promoter and other

expression control elements for expression in the tumor cells, which vector is prepared by a method comprising growing cells in a medium, providing nutrients, infection of the cells with the adenovirus vector, lysing the cells, purifying the adenovirus, and formulating such purified adenovirus and other known methods of adenoviral gene therapy,

does not reasonably provide enablement for treating any disease/disorder in any animal by administering any adenoviral vector comprising any transgene via any route, yields of adenovirus that are 70% +/- 10% of that found in the lysate by any other method than growing the cells at a low to medium perfusion rate of 1-2 g/L glucose, followed by detergent lysis with 1% Tween 20, a single anion exchange chromatography step in a Toyopearl Super Q 650 FPLC anion exchange column, and concentration/diafiltration and nuclease treatment. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims, for reasons of record.

Response to Argument – Enablement

Applicant's argument of 10/28/05 has been fully considered but is not found persuasive.

Applicant argues that the specification enables the preparation of the therapeutic compositions and practice of the methods of the claims beyond just known gene therapy methods, averring that the Examiner has not provided sufficient explanation of why it does not (Applicant's argument of 10/28/05, p. 30, paragraph 2).

Such is not persuasive. The Examiner has provided a detailed analysis of the Wands factors, and such leads to the inevitable conclusion that Applicant has not contributed anything to the art to make the methods of gene therapy with adenoviral vectors enabled for any gene

therapy beyond what is already known (e.g., Official Action of 7/13/05, pp. 24-25, paragraph bridging). To help Applicant understand, Applicant's invention is in the methods of making the adenoviral vectors, not in gene therapy, as evidenced by the specification as a whole, and the structure of the adenoviral vectors is not distinct in any way from an adenoviral vector made by the known methods in the Art; hence, the Examiner is left with the lack of reasonable predictability in the art with regard to all gene therapy with an adenoviral vector, as has been reviewed in the Official Action of 7/13/05. However, if Applicant can explain how their vectors are enabling of all gene therapy, the rejection will be dropped, but until then, in view of the fact that methods claims must be enabling for their full breadth (MPEP 2164.08 [R-1]), the claims face a scope of enablement.

Applicant argues that the PTO is required to assume that the specification complies with the enablement provisions of 35 USC 112, first paragraph, unless it has acceptable evidence or reasoning to suggest otherwise, citing Hamada, et al. (1996) Cancer Research, 56: 3047-54, to argue by way of example, that p53 may be used to treat cancers without p53 inactivation (Applicant's argument of 10/28/05, pp. 30-31).

Such is not persuasive. As is noted by Hamada, each of the cell lines, etc., exhibits at least lowered, if not completely removed, p53 expression, and in fact, Hamada makes clear that these cervical cancer cells depend on p53 and pRb inactivation in order to produce cancer (p. 3047, paragraph bridging columns). Moreover, Hamada does not even conclude that it is reasonably predictable to even treat these cervical cancer tumors, but instead, the results provide a sound basis for further research (p. 3053, last paragraph). Simply because other mutations are exhibited does not negate the fact that p53 expression/effects are present in such cells. Further,

Applicant's claims are not limited to p53 and cervical cancer, but encompass all gene therapy, by any method of administration, with any transgene and operably linked expression regulatory elements. Lastly, the Examiner has provided reason to doubt that another set of disorders could be treated, outside of cancer therapy: brain diseases (e.g., Official Action of 7/13/05, p. 16). Applicant has failed to address how the lack of enablement is overcome for even this set of diseases.

Applicant argues that the references provided in the nature of the invention of the prior official action (1) only generalize about gene therapy and (2) do not state that gene will not work. Moreover, Applicant argues their experiments demonstrate gene therapy with AdV vectors containing p53 transgenes does work.

Such is not persuasive. In the references provided, various unpredictabilities are discussed, and Applicant has not demonstrated why they are not applicable to Applicant's invention. Second, the Examiner admits that particular instances of gene therapy will work, but they are peculiar to the techniques and materials used in the gene therapy, for reasons of record (e.g., Official Action of 7/13/05, pp. 24-25, paragraph bridging). However, Applicant's claims are not limited to those therapies known to work, but any therapy under the sun, and as such, they are not enabled, as it would require undue experimentation to find the working embodiments with any reasonable predictability.

Applicant argues that Deonarain identifies targeting a sufficient population of cells, and adequate expression, and Applicant argues that their evidence overcomes such problems in the art (Applicant's argument of 10/28/05, p. 31, paragraph 3).

Such is not persuasive. Applicant has not limited their claims to gene therapy of cancers wherein p53 is a causative factor, but encompasses all gene therapy. How Applicant's demonstration, through specific administration methods overcomes the broad gene therapy problems is still not understood by the Examiner. Moreover, Deonarain is not read in a vacume but along with many other references stating the same things, and hence, while specific known therapies may be enabled, the full breadth of Applicant's claims are not enabled.

Applicant argues that Verma does not discuss Ad-p53 cancer therapy, and does not state that gene therapy requires "undue experimentation", and therefore the claims are enabled (Applicant's argument of 10/28/05, p. 31, paragraph 4).

Such is not persuasive. First, Verma is not writing for the patent law, but instead giving an overview of gene therapy. Hence, Verma would not be reasonably expected to state that gene therapy requires "undue experimentation", and even if Verma made such a statement, it is doubtful that Verma would have meant undue experimentation as regards the patent law. Second, Verma discusses various aspects of gene therapy in general, determines that many aspects, particular gene targeting, which is related to administration method, is a problem, as well as immune responses, which may negate any particular gene therapy before therapy has been effected (e.g., Official Action of 7/13/05, p. 11). Certainly, this is directly related to Applicant's broad methodology, which is not just limited to p53 encoding adenoviral vectors, but any therapy and any transgene, administered by any method. Lastly, Verma is not read in a vacumme, but instead along with many other references supplied by the Examiner, to demonstrate that the Art in general is not enabling for such a broad claim.

Applicant argues that Gorecki demonstrates specific key hurdles but does not state that the obstacles are insurmountable, and hence, Applicant's invention is enabled (Applicant's argument of 10/28/05, pp. 31-32, paragraph bridging).

Such is not persuasive. First, it is not a question if such obstacles are insurmountable, as clearly, if one were to try all gene therapies for all diseases, through all routes of administration, with all transgenes and promoters, etc., one would necessarily determine those gene therapies which would work. Instead, the question is whether it is reasonably predictable, and the Examiner has shown that the breadth is not enabled, because such experimentation would undue to reasonably predict the working embodiments (Official Action of 7/13/05).

Applicant argues that Green's identification of key hurdles are rebutted by Zhang, and therefore the claims are enabled (Applicant's argument of 10/28/05, p. 32, paragraph 2).

Such is not persuasive. Zhang only demonstrates enablement for a limited range of gene therapy (p53-inactivated tumors), and direct administration of adenoviral vectors encoding p53 (Official Action of 7/13/05, p. 15); however, Applicant wishes all therapies, and all transgenes and all methods of administration. Such is necessarily not consonant with what has been disclosed and what is discussed in that part of the rejection.

Applicant argues that Nemunaitis indicates that intravenous administration of adenoviral vectors is a "feasible approach", further confirming intravenous delivery of vectors to tumors, and Shirakawa demonstrates administration of adenovirus vectors carrying thymidine kinase, arguing that these disclosure rebut the PTO's contention that Applicant's methods are only enabled for known effective gene therapies (Applicant's argument of 10/28/05, p. 32, paragraph 3).

Such is not persuasive. Nemunaitis only demonstrates a single example of one patient which had such intra-tumoral delivery (p. 753, col. 2, paragraph 1), and uses a vector which specifically replicates only in specific tumoral cells (p. 746, last paragraph). Moreover Nemunaitis is after Applicant's date of invention, and Applicant does not even demonstrate possession of such vectors. Further, Nemunaitis does not demonstrate it to be reasonably predictable for this particular therapy, because it requires further experimentation is required to obtain consistent delivery to the tumor tissue, which requires further exploration of various approaches (p. 753, col. 2). As such, it would constitute undue experimentation, even after Neumanaitis, to determine if such therapeutic methods were enabled for even this therapy. With regard to Shirakawa, Shirakawa indicates that their methods are limited to pulmonary metastases, with tumor-specific promoters, to effect specific therapies (p. 279), and is further convoluted by the fact regional perfusion still needs to be explored to determine a reasonably predictable method of administration (p. 277), and further by the fact that Shirakawa indicates that further experimentation is required with larger models (p. 279). Hence, such would be undue experimentation to determine the specific method of administration and promoters and transgenes which would produce a therapeutic effect for this specific therapy in any animal. Moreover, Applicant's claims are not limited to this form of therapy, but to any therapy in any animal, even therapies which are not tumor therapies. Hence, as has been determined by the Official Action of 7/13/05, while known effective therapies are enabled, Applicant is enabled for any therapy (e.g., p. 24-25, paragraph bridging).

Applicant argues that the specification discloses a multitude of genes, administrations, and formulations, and therefore they are enabled for the breadth of the claimed invention (Applicant's argument of 10/28/05, pp. 32-35).

Such is not persuasive. Applicant is claiming all gene therapy, not known effective gene therapies, and the claims are not even limited to those genes, administrations, etc., which are disclosed, and as such encompass all gene therapy. Hence, for example, the Examiner has demonstrated how brain disorders are not reasonably predictable, and require undue experimentation to treat such disorders with Applicant's claimed methods (e.g., Official Action of 7/13/05, p. 16). The Examiner fails to understand how Applicant's claimed methods even overcome the issues in these forms of gene therapy, and even, having been given a laundry list of a large number of genes, and a large number of disorders, and a large number of formulations, administrations, etc., the Artisan would even be lead to any particular combination to obtain any particular therapy of any disorder (e.g., Official Action of 7/13/05, pp. 24-25, paragraph bridging). Hence, the Artisan would only be able to reasonably predict that known effective gene therapy techniques would be enabled for Applicant's claimed method.

Applicant argues that the declaration of Dr. Menander of 4/11/05 outlines many methods of AdV-p53 treatment of tumors via proposed clinical trials, and that as a general rule, the Office should presume enablement criteria are met because such clinical trials, citing MPEP 2107.03 IV (Applicant's argument of 10/28/05, pp. 35-36).

Such is not persuasive. Applicant again mistakes utility for enablement. Specifically, MPEP 2107.03 is directed to therapeutic utility, not to enablement. Applicant does not face a scope of utility, or any utility rejection whatsoever. Applicant faces a scope of enablement. If

Applicant wishes address whether they have established utility, such should be made in a separate argument. Moreover, the intertwined nature of utility and enablement are understood, and believed to be properly addressed by the Examiner. Attempts to subvert enablement with utility are not persuasive. Moreover, Applicant's methods are not limited to treating cancers with p53 encoding adenoviral vectors, but to any therapy, any transgene, any administration, and any animal. It is unclear how such p53-encoding AdV vectors to treat tumors would even correlate to all the therapies Applicant claims.

Lastly, it is noted that Applicant has provided no arguments with regard to that scope enabled for viral yields (e.g., Official Action of 7/13/05, p. 7), and has not amended the claims accordingly. Hence, this basis of rejection is maintained.

Hence, Applicant's claims remain rejected for lacking enablement for those therapies not already established in the art, and for the aforementioned scope of making viral yields of 70+/-10% of that found in the lysate.

Claim Rejections - 35 USC § 102/103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

In light of Applicant's amendments and argument, the rejections of Claims 70-71, 75-77, 83, and 85-100 under 35 U.S.C. 102(e) as being anticipated by Zhang, et al., filed 29 October 1993, patented 25 June 2002, as further evidenced by Huyghe, et al. (1995) Human Gene Therapy, 6: 1403-1416, are withdrawn;

However, Claim 73 remains rejected under 35 U.S.C. 102(e) as being anticipated by Zhang, et al., filed 29 October 1993, patented 25 June 2002, as further evidenced by Huyghe, et al. (1995) Human Gene Therapy, 6: 1403-1416, for reasons of record.

In addition, Claims 70-72, 74-78, 83, and 85-100 are newly rejected under 35 U.S.C. 102(e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Zhang, et al., filed 29 October 1993, patented 25 June 2002, as further evidenced by Huyghe, et al. (1995) Human Gene Therapy, 6: 1403-1416, under the new basis of rejection set forth below.

With regard to Claims 70-73, 97, and 100, Zhang teaches the direct administration (e.g., col. 23, lines 8-10) of adenoviral vectors (Id.) comprising the CMV-MIE promoter operably

linked to a p53 transgene (EXAMPLE 4) for treating cancer in a mouse (EXAMPLE 6). Moreover, such adenoviral vectors may lack E1A and/or E1B genes, and be grown in 293 cells (e.g., col. 4, lines 15-32). Furthermore it is desirable that such compositions are substantially pure (e.g., col. 5, lines 1-14). Lastly, such compositions are administered in a pharmaceutically-acceptable buffers, which requires formulation (Id.).

With regard to Claims 85-90, Zhang teaches an adenovirus with the exogenous encoding region for p53, operatively linked to the CMV-IE promoter (e.g., col. 4, last paragraph).

With regard to Claims 91-93, Zhang teaches vectors missing parts of E1A and/or E1B (col. 4, paragraphs 2-3).

With regard to Claims 94-95, Zhang teaches 293 host cells, which compliment the production of replication incompetent virus (col. 4, paragraph 4)

With regard to Claims 98-100, Zhang teaches that 10-50 PFU per cell will yield growth inhibition due to viral infection and expression of p53 (cols. 13-14, paragraph bridging). Moreover, Zhang teaches using $5x10^7$PFU/mouse (EXAMPLE 6), and changing the PFU administered based on the result desired (EXAMPLE 7). Therefore, Zhang inherently teaches Applicant's claimed amounts, as those amounts may be desired, for instance, to infect $50x10^{10}$ cells at 50 PFU/cell, one would use 10^{10} PFU.

With regard to all the claims subject to this rejection, Zhang does not explicitly review how to manufacture the adenoviruses, through the steps of growing host cells in a media, providing nutrients to the host cells, infecting the host cells with adenovirus, lysing said host cells, and purifying adenovirus from the lysate; although Zhang does evidence use of CsCl gradients for purification and formulation (col. 5, paragraph 1). Moreover, the other steps are

inherent in Zhang, as these are required steps for growing adenovirus for use. Huyghe evidences these aspects, as Huyghe demonstrates a standard method of making such adenoviruses, in comparison to alternative methods where chromatography substitutes for CsCl centrifugation (TITLE; pp.1407-1408). Specifically, Huyghe teaches that 293 cells are infected with adenovirus vector 2.5 days after growing host cells in media, which provides the nutrients needed to grow, as well as grow adenovirus (p. 1404, col. 1, paragraph 5); cells are lysed to yield adenovirus (Id., last paragraph), and may be purified by cesium chloride (p. 1404, col. 2-1405, col. 1). Moreover, absent to believe otherwise, such produced adenovirus is essentially pure and contains BSA levels below the detection limit of a western blot assay, and is further essentially free of BSA.

With regard to claim 71-72, Huyghe teaches such methods yield substantially pure adenoviral compositions that may be as high as 60-80% depending on the steps utilized (p. 1408, col. 1, paragraph 2).

With regard to claims 75-77, as has been demonstrated above, the required levels of contaminating nucleic acid are attained in CsCl gradient isolations, and Huyghe teaches that such CsCl gradient purifications yield an AD260/280 of between 1.2-1.3, and may reflects variability in the method, which indicates that individual experiments will yield 1.27.

With regard to claim 83, Huyghe teaches feeding the batch (e.g., p. 1404, col. 1, paragraph 5).

With regard to claims 96, 73-74, and 77, Huyghe teaches treating the lysate with nuclease (p. 1404, col. 2, paragraph 2), which Applicant demonstrates achieves the required levels of nucleic acid contamination (e.g., TABLE 10).

With regard to BSA levels (all claims, and 70 and 78 in particular), although the Art utilized does not comment on BSA levels in the compositions produced, absent reason to believe otherwise the amount of BSA present is assumed to be under the levels of detection by western blot assay, and the compositions are assumed to be essentially free of BSA.

The office does not have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. See Ex parte Phillips, 28 USPQ 1302, 1303 (BPAI 1993), In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ2d 1922, 1923 (BPAI 1989).

Response to Argument – Zhang

Applicant's argument of 10/28/05 has been fully considered but is not found persuasive.

Applicant argues that Zhang fails to teach BSA levels, and hence the rejection should be withdrawn (Applicant's argument of 10/28/05, p. 36, paragraph 2).

Such is not persuasive, as claim 73 does not require any BSA levels, and further, the new basis of rejection makes clear that all of the claims are still rejected.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

> having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 70-71, 78-82, and 84 remain rejected and claims 72-77, 83, and 85-100 are newly rejected, under 35 U.S.C. 103(a) as being unpatentable over Zhang, et al., filed 29 October 1993, patented 25 June 2002, as further evidenced by Huyghe, et al. (1995) Human Gene Therapy, 6: 1403-1416 as applied to claim 73 above, and further in view of Perrin, et al. (1995) Vaccine, 13(13): 1244-50.

With regard to Claims 70-78, 83, and 85-100, as shown above, Zhang, as evidenced by Huyghe, teaches and/or makes obvious the various aspects of the claims, however, Zhang does not teach the aspects of serum free media, bioreactors, microcarriers, or perfusion methods. Also, in order to bolster the rejection on the basis of the 103, if Applicant should demonstrate that the above methods by Zhang, as evidenced by Huyghe alone, would not produce the required levels of BSA found in the claims, this rejection is also extended to all the claims requiring such BSA levels.

On the other hand, Perrin teaches the use of serum-free media to overcome various problems (p. 1244, col. 2, paragraph 2-p. 1245, col. 1, paragraph 1). Moreover, Applicant teaches that the levels of BSA are caused by use of serum-free media (e.g., SPECIFICATION, p. 92, paragraph 2). With regard to the use of bioreactors and microcarriers, Perrin teaches that it was standard in the art to use such bioreactors with such microcarriers (p. 1244, col. 2, paragraph 2), as well as the use of perfusion techniques and roller-bottles (id.).

At the time of invention by Applicant, it would have been obvious to modify the methods of Zhang with the steps of Perrin. The Artisan would have been motivated to do so because such methods were standard in the art. Moreover, the Artisan would have had reasonable expectation

of success, as the Art had already demonstrated that such methods are successful in producing virus.

Response to Argument – Zhang/Perrin

Applicant's argument of 10/28/05 has been fully considered but is not found persuasive.

Applicant argues that Perrin does not make up for the deficiencies of Zhang, as it teaches serum free media with a rabies virus system, and avers that rabies is so distinct from adenovirus, that there would be no reasonable expectation of success (Applicant's argument of 10/28/05, pp. 36-37, paragraph bridging-p. 37, paragraph 2).

Such is not persuasive. Perrin shows that cells may be grown and produce, even in "clump" form in culture, similar to Applicant's notes that the cells forms clumps in their experiments in the absence of heparin, and the Examiner fails to understand how adenoviruses have any specific requirements distinct from rabies virus such that there would not exist a reasonable expectation of success.

Hence, the rejections are held, and newly applied. It is further noted that Applicant has gripped onto the Examiner's inadvertent error in not listing claim 72 in the previous rejections, and as such, even though clearly the limitation to "substantially purified" was covered in substance, Applicant is entitled to yet another non-final rejection.

Claim Rejections - 35 USC § 103 – Zhang, Nadeau/Trepanier

Claim 74 remains further rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang, et al., filed 29 October 1993, patented 25 June 2002, as further evidenced by Huyghe, et

al. (1995) Human Gene Therapy, 6: 1403-1416 and Nadeau, et al. (1996) Biotechnology and Bioengineering, 51: 613-623, or Trepanier, et al. (1981) J. Virological Methods, 3: 201-11.

As is shown above, Zhang, as evidenced by Huyghe, teaches the various aspects of claim 70; however, Zhang does not specifically discuss nucleic acid contaminations less than 0.2ng/mL.

On the other hand, the other two references (Nadeau and Trepanier) teach the use of ultrafiltration in the purification of viral particles (e.g., Nadeau, p. 615, col. 1, paragraph 1). As such, these steps are generally known in the art. Moreover, Applicant's specification makes clear that such ultrafiltration step yields the desired levels of contaminating nucleic acids (SPECIFICATION, TABLE 10). Hence, such ultrafiltration would necessarily yield the desired levels of contaminating nucleic acid.

At the time of invention by Applicant it would have been obvious to modify the methods of Zhang by the ultrafiltration step of either Nadeau or Trepanier. One would have been motivated to do so because such steps are known in the art for concentration and purifying adenovirus. Moreover, the Artisan would have had a reasonable expectation of success, as these methods were already known successful.

Response to Argument – Zhang, Nadeau/Trepanier

Applicant's argument of 10/28/05 has been fully considered but is not found persuasive.

Applicant argues that they have established their "method" is capable of achieving specific levels of nucleic acid contamination, and as such, there is nothing to provide motivation in the art to combine the references (Applicant's argument of 10/28/05, p. 37, paragraph 3).

Such is not persuasive. If Applicant is arguing hindsight, the Examiner does not understand how Applicant's specification is looked to in order to make the rejection. If Applicant is arguing motivation, such is not persuasive, as the Artisan would be motivated to do so because such methods are standard in the art. Moreover, absent to believe otherwise, the method would achieve Applicant's desired effects.

The office does not have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. See Ex parte Phillips, 28 USPQ 1302, 1303 (BPAI 1993), In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ2d 1922, 1923 (BPAI 1989).

Claim Rejections - 35 USC § 103 – Zhang/Perrin

Claims 101, 103-104, and 106-131 remain rejected, and claims 102 and 105 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang, et al., filed 29 October 1993, patented 25 June 2002, as further evidenced by Huyghe, et al. (1995) Human Gene Therapy, 6: 1403-1416 as applied to claims 70-78, 83, and 85-100 above, and further in view of Perrin, et al. (1995) Vaccine, 13(13): 1244-50 for reasons of record, and/or reasons delineated below.

As shown above, Zhang, as evidenced by Huyghe, teaches the various aspects of claims 70-78, 83, and 85-100; however, if Applicant should argue that Zhang does not teach the aspects of bioreactors and/or microcarriers, nor does Zhang specifically discuss BSA levels below the

detection limit of western blots or essentially free of BSA, serum free media, bioreactors, microcarriers, or perfusion methods.

On the other hand, Perrin teaches the use of serum-free media to overcome various problems (p. 1244, col. 2, paragraph 2-p. 1245, col. 1, paragraph 1). Moreover, Applicant teaches that the levels of BSA are caused by use of serum-free media (e.g., SPECIFICATION, p. 92, paragraph 2). With regard to the use of bioreactors and microcarriers, Perrin teaches that it was standard in the art to use such bioreactors with such microcarriers (p. 1244, col. 2, paragraph 2), as well as the use of perfusion techniques and roller-bottles (id.).

At the time of invention by Applicant, it would have been obvious to modify the methods of Zhang with the steps of Perrin. The Artisan would have been motivated to do so because such methods were standard in the art. Moreover, the Artisan would have had reasonable expectation of success, as the Art had already demonstrated that such methods are successful in producing virus.

Moreover, regarding BSA levels and substantial purification, although not specifically addressing the specific embodiments, the Examiner has no reason to believe that these compositions would not be substantially pure, or have the required levels of BSA. Further, even if Perrin is not used for the teaching of serum-free media, the Examiner has no reasons to believe that the required levels of BSA would not be obtained from the cultures of Zhang.

The office does not have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed

products are functionally different than those taught by the prior art and to establish patentable differences. See Ex parte Phillips, 28 USPQ 1302, 1303 (BPAI 1993), In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ2d 1922, 1923 (BPAI 1989).

Response to Argument – Zhang/Perrin

Applicant's argument has been fully considered but is not found persuasive.

Applicant argues that these rejections should be withdrawn for the same reasons as the base claims (e.g., Claim 70) under the same reasoning (Applicant's argument of 10/28/05, pp. 37-38, paragraph bridging).

Such is not persuasive. Although the reference makes no mention of the specific levels, absent reason to believe otherwise, the claims teach such levels of BSA and purity.

The office does not have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. See Ex parte Phillips, 28 USPQ 1302, 1303 (BPAI 1993), In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ2d 1922, 1923 (BPAI 1989).

Claim Rejections - 35 USC § 103

Claims 132, 134-135, and 137-162 remain, and Claims 133 and 136 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang, et al., filed 29 October 1993, patented 25 June 2002, as further evidenced by Huyghe, et al. (1995) Human Gene Therapy, 6: 1403-

1416, and Perrin, et al. (1995) Vaccine, 13(13): 1244-50, for reasons of record and reasons delineated below.

With regard to Claims 132, 134, 159 and 162, Zhang teaches the direct administration (e.g., col. 23, lines 8-10) of adenoviral vectors (Id.) comprising the CMV-MIE promoter operably linked to a p53 transgene (EXAMPLE 4) for treating cancer in a mouse (EXAMPLE 6). Moreover, such adenoviral vectors may lack E1A and/or E1B genes, and be grown in 293 cells (e.g., col. 4, lines 15-32). Furthermore it is desirable that such compositions are substantially pure (e.g., col. 5, lines 1-14). Lastly, such compositions are administered in a pharmaceutically-acceptable buffers, which requires formulation (Id.).

With regard to Claim 135, Zhang teaches the use of cesium chloride gradients in the purification of the adenovirus. Moreover, Applicant indicates that such levels of contamination are a result of cesium chloride gradient isolation (e.g., Applicant's SPECIFICATION, TABLE 10). Therefore, Zhang inherently attains the level of contamination required.

With regard to Claims 147-152, Zhang teaches an adenovirus with the exogenous encoding region for p53, operatively linked to the CMV-IE promoter (e.g., col. 4, last paragraph).

With regard to Claims 153-155, Zhang teaches vectors missing parts of E1A and/or E1B (col. 4, paragraphs 2-3).

With regard to Claims 156-157, Zhang teaches 293 host cells, which compliment the production of replication incompetent virus (col. 4, paragraph 4)

With regard to Claims 160-161, Zhang teaches that 10-50 PFU per cell will yield growth inhibition due to viral infection and expression of p53 (cols. 13-14, paragraph bridging).

Moreover, Zhang teaches using $5x10^7$PFU/mouse (EXAMPLE 6), and changing the PFU administered based on the result desired (EXAMPLE 7). Therefore, Zhang inherently teaches Applicant's claimed amounts, as those amounts may be desired, for instance, to infect $50x10^{10}$ cells at 50 PFU/cell, one would use 10^{10} PFU.

With regard to all the claims subject to this rejection, Zhang does not explicitly review how to manufacture the adenoviruses, through the steps of growing host cells in a media, providing nutrients to the host cells, infecting the host cells with adenovirus, lysing said host cells, and purifying adenovirus from the lysate; although Zhang does evidence use of CsCl gradients for purification and formulation (col. 5, paragraph 1). Moreover, the other steps are inherent in Zhang, as these are required steps for growing adenovirus for use. Huyghe evidences these aspects, as Huyghe demonstrates a standard method of making such adenoviruses, in comparison to alternative methods where chromatography substitutes for CsCl centrifugation (TITLE; pp.1407-1408). Specifically, Huyghe teaches that 293 cells are infected with adenovirus vector 2.5 days after growing host cells in media, which provides the nutrients needed to grow, as well as grow adenovirus (p. 1404, col. 1, paragraph 5); cells are lysed to yield adenovirus (Id., last paragraph), and may be purified by cesium chloride (p. 1404, col. 2-1405, col. 1).

With regard to claims 133-134, Huyghe teaches such methods yield substantially pure adenoviral compositions that may be as high as 60-80% depending on the steps utilized (p. 1408, col. 1, paragraph 2).

With regard to claims 137-139, as has been demonstrated above, the required levels of contaminating nucleic acid are attained in CsCl gradient isolations, and Huyghe teaches that such

CsCl gradient purifications yield an AD260/280 of between 1.2-1.3, and may reflects variability in the method, which indicates that individual experiments will yield 1.27.

With regard to claim 145, Huyghe teaches feeding the batch (e.g., p. 1404, col. 1, paragraph 5).

With regard to claim 158 and 135-136, Huyghe teaches treating the lysate with nuclease (p. 1404, col. 2, paragraph 2), which Applicant discloses attains the specific levels of contamination by nucleic acid (TABLE 10).

However, Zhang does not teach the aspects of perfusion, roller bottles, serum free media; bioreactors; or microcarriers. Further Zhang does not specifically discuss BSA levels below western blot detection levels and compositions essentially free of BSA, even though such compositions are, absent to believe otherwise, meeting these limitations.

On the other hand, Perrin teaches the use of serum-free media to overcome various problems (p. 1244, col. 2, paragraph 2-p. 1245, col. 1, paragraph 1). Moreover, Applicant teaches that the levels of BSA are caused by use of serum-free media (e.g., SPECIFICATION, p. 92, paragraph 2). With regard to the use of bioreactors and microcarriers, Perrin teaches that it was standard in the art to use such bioreactors with such microcarriers (p. 1244, col. 2, paragraph 2), as well as the use of perfusion techniques and roller-bottles (id.).

At the time of invention by Applicant, it would have been obvious to modify the methods of Zhang with the steps of Perrin. The Artisan would have been motivated to do so because such methods were standard in the art. Moreover, the Artisan would have had reasonable expectation of success, as the Art had already demonstrated that such methods are successful in producing virus.

Moreover, with regard to the specific levels of BSA, absent reason to believe otherwise, the methods in the art will attain the required levels of BSA.

The office does not have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. See Ex parte Phillips, 28 USPQ 1302, 1303 (BPAI 1993), In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ2d 1922, 1923 (BPAI 1989).

Response to Argument – Zhang/Perrin

Applicant's argument of 10/28/05 has been fully considered but is not found persuasive.

Applicant argues that the BSA levels are not taught by Zhang (Applicant's argument of 10/28/05, pp. 36-37, paragraph bridging).

Such is not persuasive. Absent reason to believe otherwise, the methods would necessarily attain the correct levels of BSA contamination.

The office does not have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. See Ex parte Phillips, 28 USPQ 1302, 1303 (BPAI 1993), In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ2d 1922, 1923 (BPAI 1989).

Claim Rejections - 35 USC § 103

Claim 105 remains further rejected under 35 U.S.C. 103(a) as being unpatentable over over Zhang, et al., filed 29 October 1993, patented 25 June 2002, as further evidenced by Huyghe, et al. (1995) Human Gene Therapy, 6: 1403-1416, and further in view of Perrin, et al. (1995) Vaccine, 13(13): 1244-50 as applied to claim 101 above, and further in view of Nadeau, et al. (1996) Biotechnology and Bioengineering, 51: 613-623, or Trepanier, et al. (1981) J. Virological Methods, 3: 201-11.

As is shown above, Zhang, as evidenced by Huyghe and further in view of Perrin, makes obvious the various aspects of claim 101; however, Zhang specifically address the aspect of nucleic acid contaminations less than 0.2ng/mL.

On the other hand, the other two references teach the use of ultrafiltration in the purification of viral particles (e.g., Nadeau, p. 615, col. 1, paragraph 1). As such, these steps are generally known in the art. Moreover, Applicant's specification makes clear that such ultrafiltration step yields the desired levels of contaminating nucleic acids (SPECIFICATION, TABLE 10). Hence, such ultrafiltration would necessarily yield the desired levels of contaminating nucleic acid.

At the time of invention by Applicant it would have been obvious to modify the methods of Zhang by the ultrafiltration step of either Nadeau or Trepanier. One would have been motivated to do so because such steps are known in the art for concentration and purifying adenovirus. Moreover, the Artisan would have had a reasonable expectation of success, as these methods were already known successful.

Response to Argument – Zhang, Nadeau/Trepanier

Applicant's argument of 10/28/05 has been fully considered but is not found persuasive.

Applicant argues that they demonstrated such levels of purity, and as such, the Examiner has used improper hindsight (Applicant's argument of 10/28/05, p. 37, paragraph 3).

Such is not persuasive. The method was well known in the art, and would necessarily be one method which would be used by the Artisan in purification of such adenoviruses. As such, the Examiner asserts that no such hindsight has been used.

It is noted, however, that "[a]ny judgement on obviousness is in a sense necessarily a reconstruction based on hindsight reasoning, but so long as it takes into account only knowledge which was within the level of ordinary skill in the art at the time the claimed invention was made and does not include knowledge gleaned only from applicant's disclosure, such a reconstruction is proper." In re McLaughlin, 443 F2d. 1392, 170 USPQ 209, 212 (CCPA 1971).

Claim Rejections - 35 USC § 103

Claims 163, 165-166, 168-170, 176, and 178-193 remain rejected, and claims 164, 167, and 171 are newly rejected, under 35 U.S.C. 103(a) as being unpatentable over Zhang, et al., filed 29 October 1993, patented 25 June 2002, as further evidenced by Huyghe, et al. (1995) Human Gene Therapy, 6: 1403-1416, and in view of Graham, et al. (1991) Methods in Molecular Biology, vol. 7, Ed. By Murray, published by Humana Press, Inc., Clifton, NJ., pp. 109-128, for reasons of record and/or the reasons below.

With regard to Claims 163, 165, 171, 190, and 193, Zhang teaches the direct administration (e.g., col. 23, lines 8-10) of adenoviral vectors (Id.) comprising the CMV-MIE

promoter operably linked to a p53 transgene (EXAMPLE 4) for treating cancer in a mouse (EXAMPLE 6). Moreover, such adenoviral vectors may lack E1A and/or E1B genes, and be grown in 293 cells (e.g., col. 4, lines 15-32). Furthermore it is desirable that such compositions are substantially pure (e.g., col. 5, lines 1-14). Also, such compositions are administered in a pharmaceutically-acceptable buffers, which requires formulation (Id.). Lastly, absent reason to believe otherwise, the purified compositions obtain the required levels of BSA contamination.

With regard to Claim 166, Zhang teaches the use of cesium chloride gradients in the purification of the adenovirus. Moreover, Applicant indicates that such levels of contamination are a result of cesium chloride gradient isolation (e.g., Applicant's SPECIFICATION, TABLE 10). Therefore, Zhang inherently attains the level of contamination required.

With regard to Claims 178-183, Zhang teaches an adenovirus with the exogenous encoding region for p53, operatively linked to the CMV-IE promoter (e.g., col. 4, last paragraph).

With regard to Claims 184-186, Zhang teaches vectors missing parts of E1A and/or E1B (col. 4, paragraphs 2-3).

With regard to Claims 187-188, Zhang teaches 293 host cells, which compliment the production of replication incompetent virus (col. 4, paragraph 4)

With regard to Claims 191-192, Zhang teaches that 10-50 PFU per cell will yield growth inhibition due to viral infection and expression of p53 (cols. 13-14, paragraph bridging). Moreover, Zhang teaches using $5x10^7$PFU/mouse (EXAMPLE 6), and changing the PFU administered based on the result desired (EXAMPLE 7). Therefore, Zhang inherently teaches

Applicant's claimed amounts, as those amounts may be desired, for instance, to infect $50x10^{10}$ cells at 50 PFU/cell, one would use 10^{10} PFU.

With regard to 193, these patients have the cancer which is being treated, hence, they are cancer patients.

With regard to all the claims subject to this rejection, Zhang does not explicitly review how to manufacture the adenoviruses, through the steps of growing host cells in a media, providing nutrients to the host cells, infecting the host cells with adenovirus, lysing said host cells, and purifying adenovirus from the lysate; although Zhang does evidence use of CsCl gradients for purification and formulation (col. 5, paragraph 1). Moreover, the other steps are inherent in Zhang, as these are required steps for growing adenovirus for use. Huyghe evidences these aspects, as Huyghe demonstrates a standard method of making such adenoviruses, in comparison to alternative methods where chromatography substitutes for CsCl centrifugation (TITLE; pp.1407-1408). Specifically, Huyghe teaches that 293 cells are infected with adenovirus vector 2.5 days after growing host cells in media, which provides the nutrients needed to grow, as well as grow adenovirus (p. 1404, col. 1, paragraph 5); cells are lysed to yield adenovirus (Id., last paragraph), and may be purified by cesium chloride (p. 1404, col. 2-1405, col. 1).

With regard to claims 164-165, Huyghe teaches such methods yield substantially pure adenoviral compositions that may be as high as 60-80% depending on the steps utilized (p. 1408, col. 1, paragraph 2).

With regard to claims 166 and 168-170, as has been demonstrated above, the required levels of contaminating nucleic acid are attained in CsCl gradient isolations, and Huyghe teaches

that such CsCl gradient purifications yield an AD260/280 of between 1.2-1.3, and may reflects variability in the method, which indicates that individual experiments will yield 1.27.

With regard to claim 176, Huyghe teaches feeding the batch (e.g., p. 1404, col. 1, paragraph 5).

With regard to claim 189 and 166 and 167, Huyghe teaches treating the lysate with nuclease (p. 1404, col. 2, paragraph 2), which Applicant teaches attains the correct levels of contaminating nucleic acid (TABLE 10).

However, Zhang does not teach the aspect of lysing the cells containing the adenovirus by a method other than free-thaw methods.

On the other hand, Graham teaches that it is known in the art to use 5% sodium deoxycholate, which disrupts the cells without disrupting the virions (e.g., p. 119, paragraph 1).

Hence, at the time of invention by Applicant, it would have been obvious to modify the methods of Zhang with the cell disruption technique of Graham. The Artisan would have been motivated to do so because such methods disrupts the cells without disrupting the virions. Moreover, the Aritsan would have had a reasonable expectation of success, because Zhang had already grown the virions, and Graham had demonstrated that it was known in the art to lyse the cells by such technique.

Moreover, with regard to contamination with BSA and BSA levels, absent reason to believe otherwise, these compositions are assumed to have the required levels of BSA, even without the use of serum free media.

The office does not have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not

possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. See Ex parte Phillips, 28 USPQ 1302, 1303 (BPAI 1993), In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ2d 1922, 1923 (BPAI 1989).

Response to Argument – Zhang/Graham

Applicant's argument of 10/28/05 has been fully considered but is not found persuasive.

Applicant argues that Perrin fails to teach serum free media in the context of preparing adenoviruses (Applicant's argument of 10/28/05, pp. 37-38, paragraph bridging).

Such is not persuasive. These rejections do not require the use of Perrin.

Claim Rejections - 35 USC § 103

Claims 171-175 and 177 remain and Claims 163-170 and 178-193 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang, et al., filed 29 October 1993, patented 25 June 2002, as further evidenced by Huyghe, et al. (1995) Human Gene Therapy, 6: 1403-1416, and Graham, et al. (1991) Methods in Molecular Biology, vol. 7, Ed. By Murray, published by Humana Press, Inc., Clifton, NJ., pp. 109-128 as applied to claims 163-171 and 178-193, above, and further in view of Perrin, et al. (1995) Vaccine, 13(13): 1244-50.

As shown above, Zhang and Graham obviate the limitations of the claims 163-171, and 178-197, as further evidenced by Huyghe; however, they do not teach the aspects of bioreactors and/or microcarriers, they do not teach serum free media, bioreactors, microcarriers, or perfusion methods. Further, Zhang and Graham do not specifically teach BSA levels below the detection

limit of western blots or essentially free of BSA, even though, absent to believe otherwise, the compositions meet these claims. However, Perrin is now used to specifically teach these limitations.

On the other hand, Perrin teaches the use of serum-free media to overcome various problems (p. 1244, col. 2, paragraph 2-p. 1245, col. 1, paragraph 1). Moreover, Applicant teaches that the levels of BSA are caused by use of serum-free media (e.g., SPECIFICATION, p. 92, paragraph 2). With regard to the use of bioreactors and microcarriers, Perrin teaches that it was standard in the art to use such bioreactors with such microcarriers (p. 1244, col. 2, paragraph 2), as well as the use of perfusion techniques and roller-bottles (id.).

At the time of invention by Applicant, it would have been obvious to modify the methods of Zhang and Graham with the steps of Perrin. The Artisan would have been motivated to do so because such methods were standard in the art. Moreover, the Artisan would have had reasonable expectation of success, as the Art had already demonstrated that such methods are successful in producing virus.

Response to Argument – Zhang/Graham/Perrin

Applicant's argument of 10/28/05 has been fully considered but is not found persuasive.

Applicant relies on the base rejection, that of Zhang/Graham for this rejection, and such is not persuasive for the same reasons (ABOVE).

Claim Rejections - 35 USC § 103

Claim 167 remains further rejected under 35 U.S.C. 103(a) as being unpatentable Zhang, et al., filed 29 October 1993, patented 25 June 2002, as further evidenced by Huyghe, et al.

(1995) Human Gene Therapy, 6: 1403-1416, and in view of Graham, et al. (1991) Methods in Molecular Biology, vol. 7, Ed. By Murray, published by Humana Press, Inc., Clifton, NJ., pp. 109-128, or as further referenced by Perrin, above, and further in view of Nadeau, et al. (1996) Biotechnology and Bioengineering, 51: 613-623, or Trepanier, et al. (1981) J. Virological Methods, 3: 201-11.

As is shown above, Zhang, as evidenced by Huyghe and further in view of Graham and optionally further in view of Perrin, makes obvious the various aspects of claim 163; however, Zhang does not specifically teach or make obvious the aspect of nucleic acid contaminations less than 0.2ng/mL.

On the other hand, the other two references teach the use of ultrafiltration in the purification of viral particles (e.g., Nadeau, p. 615, col. 1, paragraph 1). As such, these steps are generally known in the art. Moreover, Applicant's specification makes clear that such ultrafiltration step yields the desired levels of contaminating nucleic acids (SPECIFICATION, TABLE 10). Hence, such ultrafiltration would necessarily yield the desired levels of contaminating nucleic acid.

At the time of invention by Applicant it would have been obvious to modify the methods of Zhang by the ultrafiltration step of either Nadeau or Trepanier. One would have been motivated to do so because such steps are known in the art for concentration and purifying adenovirus. Moreover, the Artisan would have had a reasonable expectation of success, as these methods were already known successful.

Response to Argument – Zhang, Nadeau/Trepanier

Applicant's argument of 10/28/05 has been fully considered but is not found persuasive.

Applicant argues that they have established their "method" is capable of achieving specific levels of nucleic acid contamination, and as such, there is nothing to provide motivation in the art to combine the references (Applicant's argument of 10/28/05, p. 37, paragraph 3).

Such is not persuasive. If Applicant is arguing hindsight, the Examiner does not understand how Applicant's specification is looked to in order to make the rejection. If Applicant is arguing motivation, such is not persuasive, as the Artisan would be motivated to do so because such methods are standard in the art. Moreover, absent to believe otherwise, the method would achieve Applicant's desired effects.

The office does not have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. See Ex parte Phillips, 28 USPQ 1302, 1303 (BPAI 1993), In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ2d 1922, 1923 (BPAI 1989).

Claim Rejections - 35 USC § 103

Claims 194, 196-197, 199-201, 207, and 209-226 remain rejected and claims 195, 198, 202 rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang, et al., filed 29 October 1993, patented 25 June 2002, and Huyghe, et al. (1995) Human Gene Therapy, 6: 1403-1416, and as further evidenced by Huyghe, for reasons of record and/or reasons provided below.

With regard to Claims 194, 196, 221, and 224, Zhang teaches the direct administration (e.g., col. 23, lines 8-10) of adenoviral vectors (Id.) comprising the CMV-MIE promoter operably linked to a p53 transgene (EXAMPLE 4) for treating cancer in a mouse (EXAMPLE 6). Moreover, such adenoviral vectors may lack E1A and/or E1B genes, and be grown in 293 cells (e.g., col. 4, lines 15-32). Furthermore it is desirable that such compositions are substantially pure (e.g., col. 5, lines 1-14). Lastly, such compositions are administered in a pharmaceutically-acceptable buffers, which requires formulation (Id.).

With regard to Claim 197, Zhang teaches the use of cesium chloride gradients in the purification of the adenovirus. Moreover, Applicant indicates that such levels of contamination are a result of cesium chloride gradient isolation (e.g., Applicant's SPECIFICATION, TABLE 10). Therefore, Zhang inherently attains the level of contamination required.

With regard to Claims 209-214, Zhang teaches an adenovirus with the exogenous encoding region for p53, operatively linked to the CMV-IE promoter (e.g., col. 4, last paragraph).

With regard to Claims 215-217, Zhang teaches vectors missing parts of E1A and/or E1B (col. 4, paragraphs 2-3).

With regard to Claims 218-219, Zhang teaches 293 host cells, which compliment the production of replication incompetent virus (col. 4, paragraph 4)

With regard to Claims 222-223, Zhang teaches that 10-50 PFU per cell will yield growth inhibition due to viral infection and expression of p53 (cols. 13-14, paragraph bridging). Moreover, Zhang teaches using $5x10^7$PFU/mouse (EXAMPLE 6), and changing the PFU administered based on the result desired (EXAMPLE 7). Therefore, Zhang inherently teaches

Applicant's claimed amounts, as those amounts may be desired, for instance, to infect $50x10^{10}$ cells at 50 PFU/cell, one would use 10^{10} PFU.

With regard to all the claims subject to this rejection, Zhang does not explicitly review how to manufacture the adenoviruses, through the steps of growing host cells in a media, providing nutrients to the host cells, infecting the host cells with adenovirus, lysing said host cells, and purifying adenovirus from the lysate; although Zhang does evidence use of CsCl gradients for purification and formulation (col. 5, paragraph 1). Moreover, the other steps are inherent in Zhang, as these are required steps for growing adenovirus for use. Huyghe evidences these aspects, as Huyghe demonstrates a standard method of making such adenoviruses, in comparison to alternative methods where chromatography substitutes for CsCl centrifugation (TITLE; pp.1407-1408). Specifically, Huyghe teaches that 293 cells are infected with adenovirus vector 2.5 days after growing host cells in media, which provides the nutrients needed to grow, as well as grow adenovirus (p. 1404, col. 1, paragraph 5); cells are lysed to yield adenovirus (Id., last paragraph), and may be purified by cesium chloride (p. 1404, col. 2-1405, col. 1).

With regard to claim 195-196, Huyghe teaches such methods yield substantially pure adenoviral compositions that may be as high as 60-80% depending on the steps utilized (p. 1408, col. 1, paragraph 2).

With regard to claims 199-201, as has been demonstrated above, the required levels of contaminating nucleic acid are attained in CsCl gradient isolations, and Huyghe teaches that such CsCl gradient purifications yield an AD260/280 of between 1.2-1.3, and may reflects variability in the method, which indicates that individual experiments will yield 1.27.

With regard to claim 207, Huyghe teaches feeding the batch (e.g., p. 1404, col. 1, paragraph 5).

With regard to claims 220 and 197-198 and 201, Huyghe teaches treating the lysate with nuclease (p. 1404, col. 2, paragraph 2), which Applicant teaches attains the required levels of contaminating nucleic acid (TABLE 10).

With regard to claims 225-226, Huyghe teaches the use of a single anion-exchange chromatography steps (p. 1405, col. 2, paragraph 3-p. 1406, paragraph 2) for isolation.

Hence, at the time of invention by Applicant, it would have been obvious to modify the methods of Zhang with the steps of Huyghe. The Artisan would have been motivated to do so because such alternative steps were known, standard protocols in the art. Moreover, the Artisan would have had a reasonable expectation of success, because Zhang had taught the methods of treatment, and Huyghe had demonstrated the methods to be successful in isolating the virus particles.

With regard the requirement for levels of BSA below detection limit of western blot assays, and being essentially free of BSA (Claims 194 and 202), absent reason to believe otherwise, these methods are assumed to attain the required levels of BSA.

The office does not have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable

differences. See Ex parte Phillips, 28 USPQ 1302, 1303 (BPAI 1993), In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ2d 1922, 1923 (BPAI 1989).

Response to Argument – Zhang/Huyghe

Applicant's argument of 10/28/05 has been fully considered but is not found persuasive.

Applicant makes not specific arguments on these rejections, but it is noted that arguments in the other rejections are similarly rebutted.

Claim Rejections - 35 USC § 103

Claims 194, 202-206, and 208 remain rejected and Claims 195-201, 207, and 209-226 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang, et al., filed 29 October 1993, patented 25 June 2002, and Huyghe, et al. (1995) Human Gene Therapy, 6: 1403-1416, and as further evidenced by Huyghe, as applied to claim 194 above, and further in view of Perrin, et al. (1995) Vaccine, 13(13): 1244-50, for reasons of record and/or reasons delineated below.

As demonstrated above, Zhang and Huyghe obviate the limitations of claim 194, however, they do not specifically teach, serum free media, bioreactors, microcarriers, perfusion techniques, or roller bottles. Moreover, with regard to BSA levels, while the references themselves, absent to believe otherwise, produce the required levels of BSA, Perrin further makes obvious the specific aspects of BSA levels.

On the other hand, Perrin teaches the use of serum-free media to overcome various problems (p. 1244, col. 2, paragraph 2-p. 1245, col. 1, paragraph 1). Moreover, Applicant teaches that the levels of BSA are caused by use of serum-free media (e.g., SPECIFICATION, p.

92, paragraph 2). With regard to the use of bioreactors and microcarriers, Perrin teaches that it was standard in the art to use such bioreactors with such microcarriers (p. 1244, col. 2, paragraph 2), as well as the use of perfusion techniques and roller-bottles (id.).

At the time of invention by Applicant, it would have been obvious to modify the methods of Zhang and Huyghe with the steps of Perrin. The Artisan would have been motivated to do so because such methods were standard in the art. Moreover, the Artisan would have had reasonable expectation of success, as the Art had already demonstrated that such methods are successful in producing virus.

Response to Argument – Zhang/Huyghe/Perrin

While Applicant makes not specific arguments to these rejections, it is noted that the arguments have been addressed with reference to the other rejections above.

Claim Rejections - 35 USC § 103

Claim 198 remains further rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang, et al., filed 29 October 1993, patented 25 June 2002, and Huyghe, et al. (1995) Human Gene Therapy, 6: 1403-1416, and/or as further referenced by Perrin (ABOVE), and further in view of Nadeau, et al. (1996) Biotechnology and Bioengineering, 51: 613-623, or Trepanier, et al. (1981) J. Virological Methods, 3: 201-11.

As is shown above, Zhang, as evidenced by Huyghe, makes obvious the various aspects of claim 194; however, Zhang does not teach or make obvious the aspect of nucleic acid contaminations less than 0.2ng/mL.

On the other hand, the other two references teach the use of ultrafiltration in the purification of viral particles (e.g., Nadeau, p. 615, col. 1, paragraph 1). As such, these steps are generally known in the art. Moreover, Applicant's specification makes clear that such ultrafiltration step yields the desired levels of contaminating nucleic acids (SPECIFICATION, TABLE 10). Hence, such ultrafiltration would necessarily yield the desired levels of contaminating nucleic acid.

At the time of invention by Applicant it would have been obvious to modify the methods of Zhang by the ultrafiltration step of either Nadeau or Trepanier. One would have been motivated to do so because such steps are known in the art for concentration and purifying adenovirus. Moreover, the Artisan would have had a reasonable expectation of success, as these methods were already known successful.

Response to Argument – Zhang/Hughe/Nadeau/Trepanier

Applicant makes no specific arguments to this rejection, but the Nadeau/Trepanier rejections have been addressed above.

Conclusion

No Claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert M. Kelly, Art Unit 1633, whose telephone number is (571) 272-0729. The examiner can normally be reached on M-F, 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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